Extracellular Nicotinamide phosphoribosyltransferase (eNAMPT) is released from tumours and is an active player in tumour microenvironment

A. A. Grolla[1], S. Torretta[1], I. Gnemmi[1], C. Travelli[1], G. Orsomando[2], P. L. Canonico[1], A. A. Genazzani[1]

[1] Department of Pharmaceutical Sciences and Department of Medical Sciences, Università del Piemonte Orientale, Novara, Italy
[2] Section of Biochemistry, Department of Clinical Sciences, Polytechnic University of Marche, Ancona

Nicotinamide phosphoribosyl transferase (NAMPT) is a protein involved in a broad range of disorders, including cancer. Its ubiquitous role is due to the double face of NAMPT: it is an intracellular protein with enzymatic activity involved in NAD metabolism (iNAMPT) as well as a released cytokine-like protein (eNAMPT). eNAMPT has been reported elevated in a variety of inflammatory and metabolic disorders, and specifically cancer patients show high serum level of this protein, often correlated with stage progression and low overall survival. For example, in gastric cancer and in colorectal cancer serum eNAMPT has been found positively correlated with stage progression; in neurological tumours it has been found increased and correlated with tumour grade and in esophageal tumours it was found elevated and could be a predictor of mortality. Surprisingly, the possibility that eNAMPT can be actively secreted by tumours, thereby contributing to modifying the microenvironment, has not been formally investigated.

Recently, we have accumulated data showing that eNAMPT is released by many cancer cell lines (melanoma, neuroblastoma cells, colon cancer cells, prostate carcinoma, glioblastoma, mesotelioma, cervical cancer). Mainly, we demonstrate for the first time in any cancer type, that eNAMPT levels in plasma of tumour-bearing mice increase and that this increase can be reconducted to the tumour itself. Indeed, B16 melanoma cells, stably expressing recombinant protein FLAG-NAMPT and injected s.c. in right flank of C57BL/6 mice, release FLAG-NAMPT directly into plasma, in a tumour volume-dependent manner. This provides an important cue on previous observations that eNAMPT is increased in patients with cancer.

Moreover, eNAMPT released by melanoma cells, in our hands, has paracrine and autocrine effects. It activates different intracellular pathways, including STAT3, in tumoural cells and increases colony formation in anchorage-independent conditions. As paracrine effect, eNAMPT induces M1 polarization in human monocytes. Last, silencing NAMPT in melanoma cells leads to a reduction in the tumour growth rate.

Our findings extend the basis to consider eNAMPT as a cytokine involved in tumour progression.